

REMARKS

Reconsideration and allowance are requested.

Claims 1-4 and 8-26 are pending. The Examiner objected, "The claims are drawn in part to non-elected subject matter." Therefore, Applicants amend the claims in accordance thereto without prejudice to later prosecution of the canceled subject matter. The amendments are fully supported by the original disclosure and, thus, no new matter is added by their entry. For example, the term "radiations" is deleted as this limitation is not required for patentability, but deletion of this redundant term does not change the original scope of the claims.

Claims 3 and 10 were not rejected; they are reformatted as independent claims. Their allowance, as well as allowance of claims depending therefrom, is requested.

Independent claims 18 and 21 were only objected to. Their allowance, as well as allowance of claims depending therefrom, is requested because their subject matter is restricted to Sendai virus in accordance with the Examiner's requirement.

35 U.S.C. 103 – Nonobviousness

To establish a case of *prima facie* obviousness, all of the claim limitations must be taught or suggested by the prior art. See M.P.E.P. § 2143.03. A claimed invention is unpatentable if the differences between it and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art. *In re Kahn*, 78 USPQ2d 1329, 1334 (Fed. Cir. 2006) citing the legal standard provided in *Graham v. John Deere*, 148 USPQ 459 (1966). The *Graham* analysis needs to be made explicitly. *KSR v. Teleflex*, 82 USPQ2d 1385, 1396 (2007). It requires findings of fact and a rational basis for combining the prior art disclosures to produce the claimed invention. See *id.* ("Often, it will be necessary for a court to look to interrelated teachings of multiple patents . . . and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue"). The use of hindsight reasoning is impermissible. See *id.* at 1397 ("A factfinder should be aware, of course, of the distortion caused

by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning”). Thus, a *prima facie* case of obviousness under Section 103(a) requires “some rationale, articulation, or reasoned basis to explain why the conclusion of obviousness is correct.” *Kahn*, 78 USPQ2d at 1335; see *KSR*, 82 USPQ2d at 1396. A claim which is directed to a combination of prior art elements “is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art.” *Id.* at 1396. Finally, a determination of *prima facie* obviousness requires a reasonable expectation of success. See *In re Rinehart*, 189 USPQ 143, 148 (C.C.P.A. 1976).

Claims 1-2, 6-7, 9 and 12-17 were rejected under Section 103(a) as allegedly unpatentable over Kumar & Sarkar (FEBS Lett. 391:17-20, 1996) in view of Bally *et al.* (U.S. Patent 5,077,056). Applicants traverse.

Kumar & Sarkar disclose loading reconstituted Sendai viral envelopes containing only the fusion protein (i.e., F-virosomes) with lysozyme. The F-virosomes are used to target cytosolic delivery of lysozyme to F9 cells. Bally *et al.* disclose that liposomes may be used to encapsulate a chemotherapeutic agent such as bleomycin, cisplatin, fluorouracil, and cytarabine. But Applicants’ invention involves use of Sendai virus envelope vectors and at least one chemotherapeutic agent incorporated therein. The claims are patentable because combining the Kumar & Sarkar and Bally *et al.* documents does not render obvious a Sendai virus envelope vector having at least one chemotherapeutic agent incorporated therein.

The failure of Kumar & Sarkar to disclose the claimed invention is not remedied by the attempt to combine that disclosure with Bally *et al.* Among those failures are (1) differences between F-virosomes and Sendai virus envelope vectors, (2) the result that delivery by Sendai virus envelope vector was not expected by the prior art, (3) the result that administration of the Sendai virus envelope vector alone has a mild anti-cancer effect was not expected by the prior art, and (4) thus use of the Sendai virus envelope vector in combination with another cancer treatment (e.g., surgical or radiation therapy) is patentable. Applicants submit that these features of their claimed invention are sufficient to distinguish over the cited documents so any other incorrect allegations about

their disclosures are not disputed here, but the opportunity to dispute them in the future is reserved.

First, the Sendai virus used in the claimed invention is an *inactivated* Sendai virus *envelope vector* that is different from a *virus vector* or a *non-virus vector* such as liposomes. Generally, for a virus vector, there are safety concerns such as concurrent introduction of essential genes from the virus into the host, leaky expression of virus genes, immunogenicity of the virus in the host, and modification of the host genome (see “Background Art” section of US 2003/0013195 A1; already of record) that are not involved in using an inactivated Sendai virus envelope vector. Although a non-virus vector has less cytotoxicity and immunogenicity problems, a non-virus vector may also have lower *in vivo* gene transduction efficiency than a virus vector (see “Background Art” section of US 2003/0013195 A1).

Further, the virosome used in Kumar & Sarkar is prepared by purifying a virus fusion protein by centrifugation or chromatography and reconstituting the fusion protein in a lipid membrane. During reconstitution, fusion protein is not necessarily inserted into lipid membranes in a manner similar to native virus fusion protein. The orientation of the fusion protein in reconstituted membrane may be inverted and thus expose previously hidden antigens. Other virus proteins (mainly M protein) are lost during reconstitution. Therefore, the ratio of F1 and HN proteins, being necessary for the virus’ ability to fuse with the host’s cell membrane, is not maintained at a level similar to that of a wild-type Sendai virus and thus the virosome’s fusion activity is lowered disadvantageously. But the orientation of membrane proteins and the amounts of virus proteins are maintained in an inactivated Sendai virus envelope vector. As a result, the possibilities of incorrect antigen presentation and lowered *in vivo* gene transduction efficiency are avoided by using the inactivated Sendai virus envelope vector (see “Background Art” section of US 2003/0013195 A1).

Additionally, Bally *et al.* disclose only the use of a liposome composed of ordinary lipids. There is neither teaching nor suggestion relating to a virosome therein. Accordingly, there is no reason for one of ordinary skill in the art to combine the Kumar & Sarkar with Bally *et al.* documents. Even if both documents were combined as proposed

in the Action, *arguendo*, there is no reasonable expectation of success in the record to make an inactivated Sendai virus envelope vector. Therefore, the claimed invention is not obvious.

Second, the examples of Applicants' specification shows that delivery of an anti-cancer agent by inactivated Sendai virus envelope vector has unexpected advantages in comparison with the anticancer agent which is not incorporated. Cytocidal effects of the anticancer agent due to its systemic administration are avoided by using inactivated Sendai virus envelope vector (see Example 1). When the anticancer agent is incorporated in inactivated Sendai virus envelope vector, the size of solid tumors growing *in vivo* was reduced (see Examples 2 and 3). There is no evidence of record that any of these results would have been expected by the prior art.

Third, administration of inactivated Sendai virus envelope virus by itself (i.e., no anticancer agent incorporated therein) has a mild anticancer effect. Again, there is no evidence of record that this result would have been expected by the prior art.

Fourth, by using the inactivated Sendai virus envelope vector in combination with another cancer treatment such as surgical therapy or radiation therapy, excellent anti-cancer effects can be achieved (see page 8, lines 17-23, of the specification). For the aforementioned reasons, the claimed invention is not obvious in view of the cited Kumar & Sarkar and Bally *et al.* documents.

The combination of Kumar & Sarkar and Bally *et al.* does not render obvious the claimed invention because all limitations of independent claims are not fairly taught or suggested in the cited documents. Moreover, claims depending from those independent claims are also not made obvious by the documents because the limitations of claim 1 or 12 are incorporated in their dependent claims. M.P.E.P. § 2143.03 citing *In re Fine*, 5 USPQ2d 1596 (Fed. Cir. 1988).

Withdrawal of the Section 103 rejection is requested because the claimed invention would not have been obvious to the ordinarily skilled artisan at the time Applicants made their invention.

35 U.S.C. 112 – Definiteness

Claims 23-24 were rejected under Section 112, second paragraph, as being allegedly "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Applicants traverse.

The term "radiations" is deleted because this limitation is not required for patent-ability. Irradiation explicitly involves the use of radiation.

Applicants request withdrawal of the Section 112, second paragraph, rejection because the pending claims are clear and definite.

Conclusion

Having fully responded to the pending Office Action, Applicants submit that the claims are in condition for allowance and earnestly solicit an early Notice to that effect. The Examiner is invited to contact the undersigned if any further information is required.

Respectfully submitted,

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